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[From the Anatomical Laboratory of the Johns Hopkins University.]

Part II.—Experimental Lesions Produced by the Action of Dog's Serum on the Cortical Nerve-cell of the Rabbit's Brain.

(PRELIMINARY PAPER.)

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THE interest that has recently been taken in the action of a number of soluble bacterial poisons produced in the course of certain infectious diseases, and capable of inducing various epiphenomena from their effect upon the nervous system, is well attested by numerous articles from the pens of authors in the four principal languages of the civilized world. The endeavor of the majority of these workers has been to discover in the corpus of the nerve-cell certain definite changes by means of selective stains, rather than to take up the several members of the neuron and consider them separately, and, indeed, this has only recently become possible.

While it is possibly stretching a point to consider blood-serum in the light of a bacterial poison, its action upon the tissues is not dissimilar, as may be seen from the results of the examination of other organs than the cerebrum from rabbits dying of

chronic serum-poisoning, and it is highly probable that we shall eventually find in every person dying after the long-continued action of soluble poisons, whether bacterial or chemic, a class of lesions of the neuron similar to those described in this communication.

In the pathologic material from the autopsy-table we are sadly hampered by a multitude of post-mortem and other changes, which, though of great moment, are imperfectly known. Therefore, experimental material, under full control from the moment the inoculation is made, through the various stages of the experiment down to fixation and the staining and mounting of the sections, is of the utmost value in establishing a precedent for a similar class of lesions in the human being, especially as there are no wide anatomic differences between the nerve-cell of the animals used and those of man.

The material for the purposes of the study is at the present time small in amount, but as it is for the moment impossible to add to it, and as the lesions in all the sections have been very constant, and of a well-defined though new type, I have concluded to utilize what I have on hand, and add to the results at a later date. I shall, therefore, confine myself to a description of the histologic changes found, without indulging in speculative conclusions, an intention for which apology is hardly needed.

It is to my mind proved by the destructive action of poisons on the nerve-cell of the cortex that it only requires the long-continued action of almost any soluble toxin to cause destructive effects on the neuron, and that these do not call for the pres-

ence of a micro-organism. This principle may be more clearly demonstrated in subsequent papers, and it will probably eventually be shown that poisons that are supposed to be limited in their action are probably universal nerve-poisons, and that their continued action results in an extensive degradation of the entire nervous system, if only a sufficient length of time be allowed them.

In the winter of 1893, Dr. Simon Flexner, of the Pathological Laboratory of Johns Hopkins Hospital, began a series of experiments upon the action upon rabbits of blood-serum obtained from man and the dog. These researches have been continued, although an outline of the pathologic changes found after the inoculations, in connection with a series of other studies, has already been published.[1]

Briefly, Flexner found that injections of serum of 1.5 per cent. of the bodily weight of the animal experimented upon were usually fatal, death occurring either immediately or after the lapse of ten or twelve hours. Quantities equal to 1 per cent. of the bodily weight caused profound disturbances, including hemoglobinuria and albuminuria, less commonly anuria, and in a few instances immediate death. When death followed at once it was usual to find thrombi in the right side of the heart, which now and then extended into the pulmonary artery and its branches. Cases in which the death of the animal was delayed for a time were of especial interest, as they showed well-marked lesions resembling in many ways the changes described in

[1] "The Pathologic Changes Caused by Certain So-called Toxalbumins." THE MEDICAL NEWS, Aug. 4, 1894, p. 116.

connection with the toxalbumins of diphtheria, ricin, and abrin.

The organs studied were the spleen, liver, kidneys, and lymph-glands. In the acute cases the spleen showed a tolerably rich fragmentation of nuclei situated especially in the Malpighian bodies; the liver, certain foci of cellular necrosis; while the renal epithelium was degenerated and many casts blocked the kidney-tubules. Very extensive lesions were found in one animal that died on the thirteenth day. The microscopic appearances were those of chronic interstitial processes in the liver and kidney. In the latter organ the tubules were in places atrophied and surrounded by a new growth of connective tissue; in other places the tubules were dilated and their epithelial lining degenerated. In the liver the chronic changes were exceedingly well marked, and were an accurate reproduction of cirrhosis in the human being. Areas of newly formed or forming connective tissue proceeded from the portal spaces and from the capsule; newly formed bile-ducts were numerous, but what was of especial moment was the association with these changes of another process, viz., acute degenerative changes in the liver-substance, which were often distinctly the starting-places of the sclerosis. In the spleen masses of fibrous tissue were found. These changes show that the damage the serum is capable of doing is not limited to the corpuscular elements of the blood, for the tissue-cells also are not indifferent to its action.

From a later series of experiments than those just referred to, Dr. Flexner very kindly placed at my

disposal the cerebra of several of the rabbits, in order to enable me to determine if the nerve-cells suffered from the action of the serum in a manner equivalent to those of the viscera mentioned. Unfortunately for our closer knowledge of the cerebral cells, these elements do not show mitotic figures, nuclear fragmentation, and coagulation-necrosis in the same manner as the liver-cells, but with our best stains, whether chemic combinations with the cellular substance or simple dyes, they are eminently stubborn to microscopic analysis; and from the reaction of the protoplasm to the dyes we can demonstrate in cells we perforce know must be diseased only indefinite alterations in the amount of absorption of the dye by the protoplasm, especially of the chromophilic particles, and most uncommonly any definite changes in the nucleus or nucleolus. These difficulties in obtaining accurate results from minor changes in the nerve-cell probably arise from the circumstance that the nerve-cells are completed elements, incapable of regeneration, and only show alterations of a pronouncedly degenerative type.

The material for this study has to this time been the brains of three rabbits from parts of two series of serum-experiments, and, so far as the lesions of the cortical cells were determined, they were constant and identical in all the animals, though varying in intensity, seemingly according to the severity of the poisoning, as rabbit No. 2, first series *a*, which died from the result of an injection and not from the long-continued poisoning the others underwent, exhibited vastly larger numbers of normal cells than its companions in the investiga-

tion. It will be noticed in the table that this rabbit lost only about two-hundred grams in weight, and, accordingly, was not so greatly emaciated as the others. It is, at present, impossible to determine exactly what part the denutrition of the tissues plays in the production of the lesions of the nerve-cell, but I can hardly doubt that it is very secondary to the direct influence of the poison upon the cell, for in human alcoholics that show no emaciation the same kind of lesions are found, varying somewhat in intensity.

A synopsis of the histories of the rabbits comprising the basis of this study is given in the accompanying table.

Methods of Preparation and Staining.

The methods pursued in the preparation of the cerebral tissues for this investigation were similar to those made use of in Part I,[1] of these studies, namely, fixing the tissues in alcohol and in Müller's fluid, and after treatment with various anilins, hematoxylin, and silver-staining, according to the silver phospho-molybdate formula, as already given.

The control-preparations were obtained from the cerebra of two young but full-grown rabbits, treated exactly according to the same formulæ for the fixing and staining, kept for the same length of time in the hardening media, and stained exactly by the same procedure as the serum-brains, often running the two together in the same jars.

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[1] Part I, "Experimental Lesions Produced by the Action of Absolute Ethyl-alcohol on the Nerve-cells of the Rabbit's Brain," will appear in the autumn number of Brain.

Serum Rabbit Series.

Number.	Age.	Weight at beginning of experiment.	Begun inoculations.	Quantity injected.	Frequency of inoculation.	Date of death.	Weight at death.	Clinical cause of death.	Gross anatomic lesions.	Remarks.
1 Series 2, *b*.	Adult.	1700 g.	Nov. 22 1894	6 c.cm. increased to 18 c.cm.	Intervals of 2 w'ks.	Apr. 8 1895	1200 g.	Exhaustion.	Great emaciation; no visible lesions.	There were no well-marked meningeal changes in any of the rabbits.
2 Series 1, *a*.	Adult.	1700 g.	Nov. 6 1894	6 c.cm. increased to 18 c.cm.	Intervals of 2 w'ks.	May 5 1895	1500 g.	Overdose of serum.	Thrombi in heart and brain.	Injections of 12 c.cm. were fatal in control-rabbits.
3 Series 1, *b*.	Adult.	1800 g.	Nov. 6 1894	6 c.cm. increased to 18 c.cm.	Intervals of 2 w'ks.	May 31 1895	1300 g.	Exhaustion.	Great emaciation; no gross lesions.	Rabbit No. 2 died suddenly after an injection of serum.

As mentioned in the first section of these studies, there are upon the dendrons of the nerve-cells of the cortex a minimal number of thickenings or varicosities. The majority of these occur at the forkings of the dendritic branches, and rarely indeed is one to be found in the course of any of the finer branches in the normal brain. In the course of the axis-cylinder there are also knots of somewhat greater frequency, which begin at a variable interval from the cellular body, and continue through the entire intra-cortical course of the axon. Occasional varicosities of the dendron must, therefore, be held to be normal, the same holding good for the axon, although in the latter they are present in greater frequency. Since Coella, Greppin, Andriezen, and a few others have found in human brains, principally those of paralytic dements, an increased number of swellings upon the dendrons, the subject of these varicosities has attracted some little attention. Flatau[1] has quite recently discussed them at some length, and has arrived at the conclusion that they are natural.

It is quite possible to imagine that normal brains have a varying number of varicosities upon their dendrons, but when they increase vastly in size and occupy the whole dendron, they must be held to be abnormal, especially when they present a size that is incompatible with anything in the normal control-preparations; and the entire cell, with the exception of the axon, frequently shows evident signs of the presence of a destructive process. Not only are these abnormal swellings of great frequency on

[1] Archiv für Mikroskop. Anatomie, May, 1895.

the finer branches and along the stems of the pyramidal nerve-cells, but it may readily be demonstrated that the very varicosities normally present, particularly the enlargements at the branchings of the dendrons, take on this alterative process, and in themselves became tumefied. Furthermore, we have one certain sign of dendritic degeneration in the pyramidal and some other nerve-cells that seems to have entirely escaped the attention, not only of the criticisers of the value of the probable degeneration, but also of its exponents. I refer to the disappearance of the gemmules or lateral buds upon the branches of the dendrites, which takes place whenever the tumefactive process is at all advanced, or even occurs coequally with this.

I have elsewhere written more fully of the gemmule and its significance histologically, and in certain forms of dementia, and it suffices now to give a short anatomic description of one very interesting part of certain of the most important of the nerve-cells, which for some unexplained reason, possibly from defective staining, has hitherto received but little attention. The gemmule, in its most developed state, is found only on the dendrites of two classes of nerve-cells, the pyramidal or psychic cells of the cerebral cortex, and the Purkinje cells of the cerebellar cortex. Histologic differences in the appearance of the gemmules are very apparent in these two varieties of cells. With the pyramidal bodies they present very much the appearance of a thin pin with a rounded head, having its sharpened point stuck into the protoplasmic substance along the edges of the dendrons,

both the ascending and basal of the cells. They are arranged with considerable regularity along the thicker protoplasmic branches, and at a rectangle with the stem of the dendrite.

On the finer dendrites the intervals between the gemmules are slightly increased, and while preserving the same form as on the thicker branches they are slightly longer, and have less of the rectangular disposition. On the branches of the Purkinje cell the gemmules are very numerous and much more closely set together than on those of the pyramidal cell, and they give to the neuron a furry appearance. Besides these inherent characteristics, they begin by a broad base, do not increase in size as they extend outward, and terminate not in a rounded knob, but in a flattened ending that is no larger than the proximal portion of the stem. Here and there between the others single ones are found, similar in appearance to those of the cortical cells.

The function of the gemmule probably is to receive nerve-impulses from the endings of the numerous terminal nerve-fibers that seem almost to touch them, and to carry these impressions to the dendrite, and by its medium on to the cell-body. Differences in the function of the gemmule of the pyramidal and Purkinje cell are probable.

Histology of the Alcohol-hardened Serum specimens.

The staining of the sections for this portion of the study was by Nissl's methylene-blue and magenta, and hematoxylin-eosin. The only noticeable difference between the several brains was that in No.

2 the perivascular spaces contained a considerable number of polynuclear leukocytes, while in the other specimens these corpuscular bodies were absent.

The larger and medium-sized arteries have absolutely no sign of alteration in their several coats. The intermediary vessels are not at all prominent; their sheaths are normal; and the perivascular spaces, while distinct, are not dilated, and contain no foci of round cell aggregations and no hematoidin débris. The capillaries and veins are normal. The endothelium of the vessels shows no trace of swelling or other abnormality.

The staining of the nerve-elements by the Nissl methods was made as intense as possible, and the decoloration not allowed to proceed quite to the usual point, in order to leave the protoplasmic processes stained to their fullest extent. The nuclei of the nerve-cells do not seem to be shrunken or irregular in contour. Few of them are of other than the mono-nucleolar variety. This nucleolus is smooth, lies toward the center of the nuclear ring, and shows no alteration in its capability for the absorption of the anilin.

Changes in the protoplasm of the corpora of the cells are somewhat indefinite. The protoplasm takes the anilin stain well, but the chromophilic particles are not well defined, and the intervening spaces between them seem to be occupied with more of the fine granules than are present in the control-slides. No stress can be placed on these indefinite changes.

A very few of the pyramidal cells contain vacu-

oles, but not even as many as three in a section. Seldom is there any appreciable shrinkage in the protoplasmic body ascertainable. The protoplasmic arms of the cells are very finely granular. In some of them small knots are to be seen, the swelling being recognizable from the absorption of a greater quantity of the dye than is present in the portions more distant from and more proximal to the cell-body. In the swelling the fine granules become less distinct than elsewhere.

In the cerebellum there is nothing noticeable in the cells of the granular and molecular layers. A few of the Purkinje cells are vacuolated.

Histology of the Müller's Fluid-hardened Specimens.

The staining of these sections was solely by the silver phospho molybdate method. Between Brains 1 and 3 there were no microscopic differences of moment. Brain No. 2 showed a slighter degree of degenerative changes in the neurons than the others, and was especially interesting from the fact that the degenerated could always be found intermingled with approximately normal cells, affording an opportunity for an accurate comparison between the different elements. This brain was also remarkable for the beautiful staining of the nerve-elements of all the layers, which were exhibited in as perfect a manner as can ever be obtained in silver preparations, and the sections were not disfigured by the presence of precipitate, even the external margins being free.

The lesions found in all the cerebra were closely

allied to those found in the alcoholic brains that formed the basis of the first study. Cells of all layers were involved in the destructive process, the pyramidal of all varieties in the first order, then the deeper-lying elements, finally those of the extreme outer edge of the second layer and the elements of the molecular lamina.

A view of a section under low enlargement shows that the primary processes of many of the pyramidal cells no longer reach into the outer portions of the molecular lamina. Their finer dendritic branches have disappeared, while the thicker ones are filled with a multitude of coarser and finer knots, scattered with some regularity along the line of the stem. On the other hand, the thick intra-capsular portions of the dendrites have not become diseased in a similar manner, but apparently retain their integrity in so far that they are not altered in appearance by coarser changes, and seldom does the body of the cell present aught but its even, rounded contour. The basal processes are often likewise shortened, and show the knotty growths upon them like their ascending fellows.

Not every cell presents a similar degree of alteration, and according to the degree of involvement they may be divided into three classes: Cells in which the process is beginning; those in which it is moderately advanced; those in which the dendrons are very much degenerated. The normal cells in Brains 1 and 3 were comparatively infrequent; in No. 2, on the contrary, more that two-thirds of the stained cells were normal.

As the degenerative process is of similar charac-

ter among all the classes of cells, we have taken the most prominent type, the pyramidal cells, as the criterion of the whole, as they are very much easier to study than the other, and have a definite size and anatomic characteristics, as well as stain constantly.

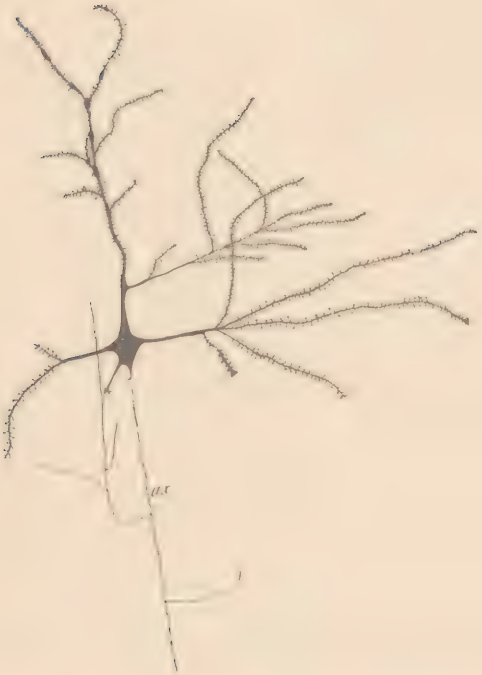
Class A, Cells Slightly Involved in the Alteration.

High up in the molecular layer we find upon the finest branches of the dendrons of the pyramidal cells, especially those of the long apical-process variety, a few tumefactions of either rounded or elongated form in the course of the stem. These tumefactions are deeply stained by the silver-salt, are smooth, and have few or no gemmules attached to their sides, or, when these are still present, there are perceptible differences in the tingeing with the silver-salt that indicate an alteration in their structure. Both nearer the cellular body and distally from the swelling, the dendrite appears to be perfectly normal, the staining is good, and the pin-like lateral buds are numerous. In these neurons the coarser branches and the corpus of the cell are undisturbed by any alteration apparent to the microscopic examination, and, indeed, the slight swellings on the finest twigs would occasion but slight comment were no other cells more deeply involved.

Class B, Cells Moderately Involved by the Degeneration.

This type is the most numerous of all. The tumefactions before present only on the finest dendritic

FIG. 1.

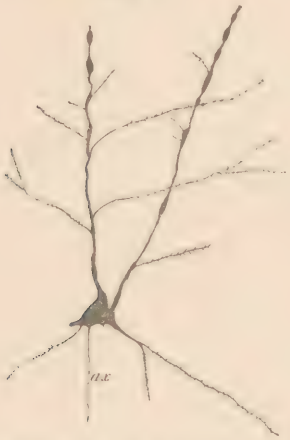


Pyramidal cell from the mid-portion of the second cellular layer of the rabbit's brain, showing commencing tumefactions of the protoplasm of the finest apical dendrites, and denudation of the gemmules at the points of swelling. At the uppermost forkings of the ascending dendron a normal enlargement of the protoplasm is seen, which is covered with gemmules. Ax., axon.

branches now extend throughout the entire path of the stems of the apical and basal processes, reaching up or down to their intra-capsular portion, and many of the finest branches are no longer stained, and are apparently totally degenerated, having been partially or totally removed. The number of the swelling varies greatly in the different involved cells. Usually the dendrons have a large number of small thickenings along their course, and present a true moniliform appearance. Less commonly there are only a few of larger size, but the result to the nerve-process is the same. These large-sized swellings are peculiarly frequent at the forkings of the branches of the apical dendrons, where there is normally a thickening of the protoplasm. Rarely one meets with dendrons in which the smaller swellings are so numerous that they are coalesced, and only are noticeably different from the normal dendron by the irregularity in their contour and the loss of the lateral buds. In all the varieties there is an absolute loss of the gemmules on the dendritic processes, which eventually proceeds to a complete stripping of the dendron of all its fine rectangular pin-like processes. This denudation of the gemmule varies considerably on the different dendrons according to the number and advancement of the swellings. When the stem has only a few constrictions the intervening spaces usually retain some of the buds, but when the swellings are numerous or very large they progressively disappear, until in a very large number of instances not only the finest branches are stripped of them, but the thicker portions are equally bare.

Following the swelling and loss of the lateral buds comes a contraction of the protoplasm of the dendritic twigs, especially that portion not involved in the swelling, though these also eventually atrophy. In the spaces between the swellings, as the process advances, the diameter of the branch grows less and less until it is reduced to a mere knotted thread.

FIG. 2.



A cell of different form from the same region of the cortex, showing an increased number of swellings and greater loss of gemmules.

Then comes a time when there is a breaking up of the continuity of the twig. The finest branches fall off from the thicker stems, and are finally absorbed, the neuron now being reduced to the corpus of the cell, with the stumpy tumefied remains of the thicker dendrons attached to it.

I wish particularly to draw attention to the loss of the finest branches of the dendrites within the limits of the molecular layer, a region of the utmost importance in the physiologic economy of the cortex. Here the branches of the dendrons, by means of their gemmules, come into contiguity with the terminations of the nerve-fibers and end-apparatus of all descriptions belonging to the several classes of nerve-fibers, tending thitherward from the interior regions of the cortex—fibers from the cord and opposite hemisphere, fibers from the fusiform and other cells of the lowermost layers of cortical cells, collaterals from the pyramidal cells, also to some extent from the intermediary cells. Here all meet in close relation with the terminal branches of the pyramidal, and in the rabbit the bicornuate cells, and the nerve-impressions are carried through the medium of the bulbous tip of the gemmule and its stem to the protoplasm of the branch, and through this to the body of the cell.

It may be readily seen that, according to this arrangement of the fibers, no matter how small the swelling of the dendron and loss of the gemmules may be, there is an instant disruption of the close connections between dendron and nerve end-apparatus, and consequently imperfect carriage of nerve-impulses from neuron to neuron; and should the destruction proceed to any considerable extent, and involve a moderate number of the protoplasmic extensions of the nerve-cells, that a serious disturbance of the mental and motor functions of the cortex will result, ending eventu-

ally in partial or complete annulling of all the mental faculties of the animal.

None of the bodies of the cells of Class B shows any noticeable alteration in structural arrangement, the destructive process having apparently to advance to a greater degree than is found with the moderate degeneration of the dendrites.

Class C, Cells Extensively Involved in the Degeneration.

This class is almost entirely absent from the cortex of Brain No. 2, but in the other cerebra it constitutes a moderate proportion of the diseased cells, especially in Brain No. 3. The dendrons are now shortened to mere stumps; the finer branches have entirely disappeared; the coarser ones are irregular in outline and have large and small swellings upon them, and are much thinned, very often terminating in an enlargement at a short distance from the cell-body, having a thin, pointed projection extending out of it in the direction of the line of the former process. The gemmules have now entirely disappeared, not a single one being visible on the portions of the dendrites that remain. The cell-body presents under these conditions two entirely different appearances, even when the dendrites are disintegrated equally. In the first one the cell-body, where the processes have almost disappeared, retains its smooth and rounded form; seldom, indeed, is it roughened, and to all appearances the condition is one of health. In the other class the protoplasmic extensions have the same general aspect, but now the corpus is distinctly involved in

Zeiss, ocular 4, objective E.

the destructive metamorphosis. The edges of the cell are roughened and irregularly eroded; deep excavations proceed from the periphery toward the central regions of the body; and, in exceptional and very advanced instances, nothing but a mass of detritus, blackened by the silver-salt, is seen occupying the site of the cell-body. In the last event nothing but the barest traces of the prolongations of the cell are to be found.

FIG. 6.

Micro-photograph of a stout ascending process of a large normal pyramidal cell, showing the arrangement of the lateral buds. A number of finer dendrons are included in the photograph. The fine granular lines indicate dendrons and vessels that were not fully in the focus of the camera.

The nerve-fibers of the layers are quite freely stained in many of our sections, but even when the degeneration of the dendrons or of the cell-body is particularly well marked there is no lesion of this portion of the neuron. Cells that are greatly frayed

FIG. 7. FIG. 8.

Fig. 7.—Micro-photograph of the finer portion of the ascending process of a normal long-stemmed pyramidal cell, showing the arrangement of the gemmules.

Fig. 8.—Ascending process of a pyramidal cell from a serum-brain from the same level as Fig. 7. The tumefactions and loss of the gemmules are very distinctly shown.

FIG. 9.

Portion of the long process of a pyramidal cell from a serum-brain, showing a swelling in the normal enlargement at the bifurcation, loss of the gemmules over it, and large knots at the ends of the four branches. Enlargement about 700 diameters.

and eroded in their bodies have perfect neurocytes, and these may be traced far downward into the

white medullary layers. Cells that are apparently almost totally destroyed are too few in number to allow of any accurate knowledge of their axon. The collaterals of the axis-cylinders of the pyramidal cells may be followed to their bulbous free extremities; nor do fibers coming from more distant regions and passing upward, to terminate in the molecular lamina, show anything but a perfectly natural condition. There is no increase of varicosity, no breaks in the staining of the nerve-thread, no difference in the appearance of the terminal apparatus.

Cortex of the Cerebellum.

The changes in the nerve-bodies resemble those in the cerebrum, but are less intense. The twigs of the Purkinje cells are often bared of their protoplasmic fur, have an occasional swelling, but are not highly degenerated. Normal Purkinje cells preponderate over abnormal ones. The free extremities of the dendrons show the alterations to a greater extent than the ones closer to the corpus of the cell, as if the swelling were just beginning. The neuraxons of these bodies are distinct and perfect. The *Korbzellen* stain infrequently, and nothing definite can be said of them. The Golgi cells are well shown, but alterations in them are slight.

Very numerous axons from the *Korbzellen*, Golgi and recurrent branches of the Purkinje cells are well stained in the molecular layer, but show nothing abnormal. Some beautiful specimens of the arborescent endings of the fibers intermingling and terminating among the branches of the Purkinje cells were found, but they also were perfectly normal,

to all indications. The neurogliar structures, both in cerebrum and cerebellum, stained in numbers neither above nor below the control, and show no structural changes in their protoplasm deviating from the normal preparations. The degeneration of the nerve-cells is, therefore, probably a simple non-inflammatory process, unaccompanied by any proliferation of the supporting elements.

While the small number of the pathologic serum-brains does not allow us to speak with entire positiveness of the lesions of the cortical cells, yet from their constancy in all our preparations it is more than probable that we have found a new class of degenerative changes of the nerve-cell that will ultimately prove of the greatest importance in a long series of irritative abnormal conditions in the human subject, and will also open up a new field for the student of mental changes.

The absence of vascular lesions of importance precludes the possibility that alterations of nutrition from disease of the vessels are of the first importance in the production of the degeneration of the dendron. Much rather would we refer them to the direct action of the toxalbumin upon the cellular protoplasm, causing, in some unknown manner, at first swelling of the substance of the dendron, and later atrophy and destruction.